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## Stem Cells and Lung Regeneration.

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**Authors:** Kalpaj R Parekh, Janna Nawroth, Albert Pai, Shana M Busch, Christiana N Senger, Amy L Ryan

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### Public Summary:

The ability to replace defective cells in an airway with cells that can engraft, integrate and restore a functional epithelium could potentially cure a number of lung diseases. Progress toward the development of strategies to regenerate the adult lung by either in vivo or ex vivo targeting of endogenous stem cells or pluripotent stem cell derivatives, is limited by our fundamental lack of understanding of the mechanisms controlling human lung development, the precise identity and function of human lung stem and progenitor cell types, and the genetic and epigenetic control of human lung fate. In this review, we intend to discuss the known stem/progenitor cell populations, their relative differences between rodents and humans, their roles in chronic lung disease, and their therapeutic prospects. Additionally, we highlight the recent breakthroughs that have increased our understanding of these cell types. These advancements include novel lineage-traced animal models and single-cell RNA sequencing of human airway cells, which have provided critical information on the stem cell subtypes, transition states, identifying cell markers, and intricate pathways that commit a stem cell to differentiate or to maintain plasticity. As our capacity to model the human lung evolves, so will our understanding of lung regeneration and our ability to target endogenous stem cells as a therapeutic approach for lung disease.

### Scientific Abstract:

Summary/Abstract The ability to replace defective cells in an airway with cells that can engraft, integrate and restore a functional epithelium could potentially cure a number of lung diseases. Progress toward the development of strategies to regenerate the adult lung by either in vivo or ex vivo targeting of endogenous stem cells or pluripotent stem cell derivatives, is limited by our fundamental lack of understanding of the mechanisms controlling human lung development, the precise identity and function of human lung stem and progenitor cell types, and the genetic and epigenetic control of human lung fate. In this review, we intend to discuss the known stem/progenitor cell populations, their relative differences between rodents and humans, their roles in chronic lung disease, and their therapeutic prospects. Additionally, we highlight the recent breakthroughs that have increased our understanding of these cell types. These advancements include novel lineage-traced animal models and single-cell RNA sequencing of human airway cells, which have provided critical information on the stem cell subtypes, transition states, identifying cell markers, and intricate pathways that commit a stem cell to differentiate or to maintain plasticity. As our capacity to model the human lung evolves, so will our understanding of lung regeneration and our ability to target endogenous stem cells as a therapeutic approach for lung disease.

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